

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205552Orig1s000

CHEMISTRY REVIEW(S)

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Application:	NDA 205552/000	Sponsor:	PHARMACYCLICS INC
OTC Code:	161		995 EAST ARQUES AVE
Priority:	1		SUNNYVALE, CA 940854521
Stamp Date:	28-JUN-2013	Brand Name:	IBRUTINIB (PCI-32765)
PDUFA Date:	28-FEB-2014	Estab. Name:	
Action Goal:		Generic Name:	IBRUTINIB (PCI-32765)
District Goal:	28-OCT-2013	Product Number; Dosage Form; Ingredient; Strengths	001; CAPSULE; IBRUTINIB; 140MG

FDA Contacts:	D. LU	Prod Qual Reviewer	(HFD-150)	3017962059
	J. MARTIN	Product Quality PM	(HFV-530)	3017962072
	D. HANNER	Regulatory Project Mgr	(HFD-006)	3017964058
	J. BROWN	Team Leader		3017961652

Overall Recommendation:	ACCEPTABLE	(b) (4)	by J. WILLIAMS	()	3017964196
	PENDING		by EES_PROD		
	ACCEPTABLE		by J. WILLIAMS	()	3017964196
	PENDING		by EES_PROD		
	PENDING		by EES_PROD		
	PENDING		by EES_PROD		
	PENDING		by EES_PROD		

Establishment: CFN: (b) (4) FEI: (b) (4)

(b) (4)

DMF No: AADA:

Responsibilities: FINISHED DOSAGE LABELER
FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE TESTER

Profile: CAPSULES, PROMPT RELEASE **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 01-SEP-2013

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Er ment: CFN: (b) (4) FEI: (b) (4)
(b) (4)

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE OTHER TESTER

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 01-SEP-2013

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: CFN: (b) (4) FEI: (b) (4)
(b) (4)

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER

Profile: CAPSULES, PROMPT RELEASE **OAI Status:** NONE

L stone: OC RECOMMENDATION

Milestone Date: 20-SEP-2013

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: CFN: (b) (4) FEI: (b) (4)
(b) (4)

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE OTHER TESTER

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 12-SEP-2013

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Establishment: CFN: [REDACTED] FEI: [REDACTED] (b) (4)
[REDACTED] (b) (4)

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE OTHER TESTER

Profile: NON-STERILE API BY CHEMICAL SYNTHESIS **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 11-OCT-2013

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: CFN: [REDACTED] (b) (4) FEI: [REDACTED] (b) (4)
[REDACTED] (b) (4)

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE [REDACTED] (b) (4)
DRUG SUBSTANCE OTHER TESTER
DRUG SUBSTANCE PACKAGER

Profile: NON-STERILE API BY CHEMICAL SYNTHESIS **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 03-JUL-2013

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: CFN: [REDACTED] (b) (4) FEI: [REDACTED] (b) (4)
[REDACTED] (b) (4)

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE OTHER TESTER

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 03-JUL-2013

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment: CFN: 2952531 FEI: 1000522932
PHARMACYCLICS INC
SUNNYVALE, , UNITED STATES 940854521
DMF No: AADA:
Responsibilities: DRUG SUBSTANCE RELEASE TESTER
DRUG SUBSTANCE STABILITY TESTER
FINISHED DOSAGE RELEASE TESTER
Profile: CONTROL TESTING LABORATORY OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 15-OCT-2013
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Establishment: CFN: FEI: (b) (4)
(b) (4)
DMF No: AADA:
Responsibilities: DRUG SUBSTANCE MANUFACTURER
Profile: (b) (4) OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 17-OCT-2013
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

NDA 205-552**Imbruvica (ibrutinib) capsules, 140 mg****Pharmacyclics, Inc.****Xiao-Hong Chen, Ph.D.
Donghao (Robert) Lu, Ph.D.****Office of New Drug Quality Assessment
Division of New Drug Quality Assessment I****CMC Review of NDA 205-552****For the Division of Oncology Drug Products I (HFD-150)**

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Chemistry Review Data Sheet

1. NDA 205-552
2. REVIEW #2:
3. REVIEW DATE: 17-OCT-2013
4. REVIEWER: Donghao (Robert) Lu, Ph.D. (Drug substance)
Xiao-Hong Chen, Ph.D. (Drug product)
5. PREVIOUS DOCUMENTS:

Previous Documents

Document Date

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original NDA submission	28-Jun-2013
Amendment SN0018	09-Aug-2013
Amendment SN0021	13-Aug-2013
Amendment SN0027	23-Aug-2013
Amendment SN0029	29-Aug-2013

7. NAME & ADDRESS OF APPLICANT:

NAME:	Pharmacyclics, Inc.
ADDRESS:	995 East Arques Avenue, Sunnyvale, CA 94085
REPRESENTATIVE:	Christine Salido, Exec. Director, Regulatory Affairs
TELEPHONE:	(408) 215-3476

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Imbruvica®
- b) Non-Proprietary Name (USAN): ibrutinib

- c) Code Name/# PCI-32765, JNJ 54179060
 d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: 1
 - Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: Filed 505(b)(1)

10. PHARMACOL. CATEGORY: A potent small-molecule covalent inhibitor of Bruton's tyrosine kinase

11. DOSAGE FORM: Capsule

12. STRENGTH/POTENCY: 140 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC

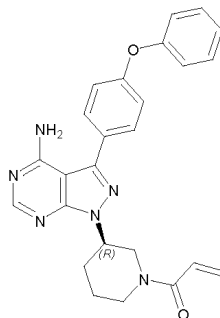
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Name (USAN, INN): Ibrutinib
 Name (CAS): 1-{(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1Hpyrazolo[3,4-d]pyrimidin-1-yl]piperidin-1-yl}prop-2-en-1-one
 Other Name: 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1Hpyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one
 (CAS) Registry Num: 936563-96-1
 Mol. Formula: C₂₅H₂₄N₆O₂
 Mol. Wt.: 440.50
 Structural Formula:



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENT
(b) (4)	III			(b) (4) 4	Adequate	8-2-2013	USP<661> and FAR (21CFR177.1520) submitted in NDA
	III			4	Adequate	8-2-2013	USP<661> and FAR (21CFR177.1520) submitted in NDA
	III			3	Adequate	1-31-2012	Reviewed by Gene Holbert
	III			4	Adequate	8-2-2013	USP<661> and FAR (21CFR177.1210) submitted in NDA
	III			3	Adequate	9-21-2012	Reviewed by Raymond P. Frankewich

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Supporting Documents:

Doc #	OWNER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS

C. Related Documents:

DOCUMENT	APPLICATION	OWNER	DESCRIPTION/COMMENT

	NUMBER		
IND	102,688	Pharmacyclics, Inc.	Original IND submitted on 07-Oct-2008.

18. CONSULTS/CMC-RELATED REVIEWS:

CONSULTS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	17-OCT-2013	Office of Compliance
Biopharmaceutics	Acceptable	25-SEP-2013	John Duan, Ph.D.
Proprietary Name	Acceptable	16-AUG-2013	Sue Kang
Methods Validation	Pending	23-JUL-2013	A methods validation request was sent and the evaluation results are pending. It should be noted that the approvability of the NDA is not dependent upon the results.
EA (Categorical exclusion)	Acceptable	13-SEP-2013	Xiao Hong Chen
Microbiology	Acceptable	9-JUL-2013	Bryan S. Riley, Ph.D.

The Chemistry Review for NDA 205-552

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From a CMC perspective, this application is recommended for Approval.

EES has an overall "Acceptable" recommendation for this NDA. Refer to the EES report in the Appendix.

Since the completion of the CMC review #1, the biopharmaceutics review of the dissolution specification has been finished and recommended "Approval" with a Post Marketing Commitment (PMC). The PMC requires the applicant to collect additional dissolution profile data (release and on stability) using the same USP Apparatus Type 2 (Paddle) at 75 rpm in a different dissolution medium from that described in the NDA. The Applicant will use the overall dissolution data to set the final dissolution acceptance criteria. The final report submission for this PMC is due on February 1, 2015. Refer to Dr. John Duan's review dated September 25, 2013 in darrrts. Review of the package insert labeling and container/carton labels has been completed. The following comment should be included in the action letter:

Based on the available stability data an 24-month expiry dating is granted for Imbruvica® ibrutinib capsules stored at temperature of 20°C to 25°C (68°F to 77°F) with excursions permitted between 15°C and 30°C (between 59°F and 86°F).

B. Recommendation on Post Marketing Requirements, Post Marketing Commitments, Agreements, and/or Risk Management Steps, if Approvable.

N/A.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Product

Ibrutinib is being co-developed by Pharmacyclics, Inc. (Pharmacyclics) and Janssen Research & Development, LLC (Janssen R&D) as an orally administered anticancer agent for the treatment of (b) (4) mantle cell lymphoma (MCL) (b) (4)

The drug product is an immediate-release opaque white size 0 hard gelatin capsule for oral administration, containing 140 mg of ibrutinib drug substance and commonly used compendial excipients such as microcrystalline cellulose, croscarmellose sodium, sodium lauryl sulfate and magnesium stearate,

etc. The drug product is packaged in two configurations: 160 cc HDPE bottles with (b) (4) child-resistant closure containing 90 capsules and 200 cc HDPE bottles containing 120 capsules.

The drug product is manufactured by the contract manufacturer, (b) (4). The intended commercial scale is (b) (4) capsules ((b) (4) total weight). Manufacturing of Ibrutinib Capsules uses (b) (4)

The drug product specifications consist of description, identity, assay, individual and total degradation products, (b) (4), content uniformity, dissolution and microbial limits. The HPLC method used for identity, assay and content uniformity is the same method that is used for the drug substance assay. The acceptance limits for the three identified degradation products have been qualified and/or below the safety threshold for oncology drugs per pharm/tox review team. The acceptance limits for degradation products (b) (4) per FDA's comments. Dissolution specification is evaluated by biopharmaceutics reviewer, Dr. John Duan. His review is still ongoing. Microbial test is reviewed by microbiology reviewer, Dr. Bryan Riley; and an acceptable recommendation was made by his review (July 8, 2013).

Stability studies for drug product are performed. Stability data for 3 registration batches, 7 primary stability batches and one supportive stability batch are submitted. The drug product appears to be fairly stable. Only a slight increasing trend of degradation products (b) (4) and a slight decreasing trend of assay have been observed. Up to 24 months long term primary and supportive stability data are well within the specification. Six months of accelerated stability data also conform to the specification with a clearer trending for degradation products and assay value. Photostability study conducted per ICH guidelines showed that the drug product is not light sensitive. Based on the primary and supportive stability data the shelf life of 24 months stored at "storage temperature at 20°C to 25°C (68°F to 77°F) with excursions permitted between 15°C and 30°C (between 59°F and 86°F) can be granted.

Drug Substance

The drug substance is Ibrutinib. The chemical name is 1-((3R)-3-[4-amino-3-(4-phenoxyphenyl)-1Hpyrazolo [3,4-d]pyrimidin-1-yl]piperidin-1-yl)prop-2-en-1-one. It has a molecular formula of C₂₅H₂₄N₆O₂ and its molecular weight is 440.50.

Data from the studies of elemental analysis, UV, IR, NMR and MS demonstrated that the structure was adequately defined. The synthesis route and the use of reagents are adequate for the manufacturing of the ibrutinib drug substance.

The impurities detected during the development and synthesis of the drug substance were evaluated. Analytical methods were developed for the control of the impurities listed in the submission. Comprehensive information for all the impurities at the starting material level, at the intermediate level and at the final synthesis level was adequately presented.

Ibrutinib was subjected to heat, heat and moisture, light, and chemical stresses. The drug substance was physically and chemically stable based on evaluation of the testing data. The drug substance has a retest period of ^(b)₍₄₎ months.

B. Description of How the Drug Product is Intended to be Used

Imbruvica® is administered by orally once daily for 560 mg (four 140 mg capsules) for MCL (Mantel cell lymphoma) patient ^(b)₍₄₎

Capsules should be taken orally with a glass of water without being opened, broken or chewed.

C. Basis for Approvability Recommendation

From a CMC perspective, Pharmacyclics, Inc. has submitted sufficient and appropriate information to support the approval of the drug product. There were several CMC concerns that were sent to the sponsor during the review process. Pharmacyclics has adequately addressed these CMC comments (see CMC review #1).

III. Administrative

A. Reviewer's Signature

See appended electronic signature page.

B. Endorsement Block

Reviewer Name/Date: Xiao-Hong Chen, Ph.D.
Donghao (Robert) Lu, Ph.D.
Branch Chief Name/Date: Ali Al Hakim, Ph.D.

C. CC Block

Diane Hanner/OHOP/DHP/Regulatory PM
Janice Brown/ONDQA/CMC Lead
Jewell Martin/ONDQA/PM
Donghao Lu/ONDQA/DNDQA I Branch II
Ali Al Hakim/ONDQA/DNDQA I/Branch Chief
Ramesh Sood/ONDQA/DNDQA I Acting Director

11 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

XIAO H CHEN
10/18/2013

DONGHAO R LU
10/18/2013

ALI H AL HAKIM
10/18/2013

Imbruvica (ibrutinib) Capsules

NDA 205-552

**Summary Basis for Recommended Action
Chemistry, Manufacturing, and Controls**

Applicant: Pharmacyclics, Inc.,
995 East Arques Avenue
Sunnyvale, CA 94085

Indication: For the treatment of [REDACTED] mantle cell
lymphoma (MCL) [REDACTED]

Presentation: The product will be available as capsules in single 140 mg strength. The capsules are packaged in two configurations: 90 count in 160 cc HDPE bottles and 120 count in 200 cc HDPE bottles.

EER Status: Pending

Consults: ONDQA Biopharmaceutics – Acceptable as per Dr. John Duan’s review dated 26-Sep-13.

Methods Validation – The methods were sent to FDA labs and the results from the lab are pending at this time. This does not affect the approvability recommendation.

EA – Categorical exclusion granted.

Microbiology- Acceptable (Bryan S. Riley, 9-Jul-13)

Post-Approval Agreements/Commitment: The biopharm reviewer has recommended a post-approval commitment. The applicant will collect additional dissolution profile data using the recommended dissolution media from at least an additional ten batches through 12 month of storage under long-term conditions. Based on these data, the applicant will set final dissolution acceptance criteria and submit this information under a supplement. The details have been included in the biopharm review by Dr. Duan.

Drug Substance:

The drug substance, ibrutinib, is a new molecular entity. It has one chiral center with R-configuration, and a molecular weight of 440.5. The drug substance is a white to off-white (b) (4) powder. (b) (4)

The CMC information for the drug substance has been reviewed and found acceptable by the reviewer. The drug substance quality is ensured through appropriate controls for the starting materials, in-process controls throughout the manufacturing process and the appropriate final drug substance specification. The drug substance specification includes tests and acceptance criteria for drug substance critical quality attributes, e.g., appearance, identification, assay, impurities, particle size distribution, crystal form, residual solvents, heavy metals, and residue on ignition. The analytical procedures have been adequately described and validated to control the quality of the drug substance. The stability of the drug substance has been demonstrated through appropriate stability studies to support a proposed retest period of (b) (4) months.

Drug product:

Imbruvica (ibrutinib) capsules are immediate release, hard gel capsules containing 140 mg of the drug substance. The drug product formulation uses standard compendial excipients. The manufacturing process includes (b) (4). The applicant has used conventional in-process controls with appropriate set points and ranges for the process parameters, and end product testing to control the quality of the drug product. The end product specification includes testing for appearance, identification, assay, content uniformity, dissolution, (b) (4), microbial contents and degradation products. The analytical procedures for the drug product testing are adequately described and validated. The provided stability data support a proposed 24-month expiration period for this product.

The drug product is stored at 20°C -25°C (68-77°F). Excursions permitted 15-30°C (59-86°F).

Conclusion: Adequate from CMC perspective.

Additional Items:

All associated Drug Master Files are acceptable or the pertinent information has been adequately provided in the application.

Overall Conclusion: The final recommendation from the Office of Compliance (OC) is pending at the time of writing this memorandum. All CMC related issues have been resolved. The application is recommended for “**Approval**” from CMC perspective

pending overall “Acceptable” recommendation from OC. A memorandum with final overall recommendation will be entered into DARRTS after the OC recommendation.

Ramesh K. Sood, Ph.D.
Division Director (Acting), DPA I/ONDQA

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RAMESH K SOOD
10/04/2013

NDA 205-552**Imbruvica (ibrutinib) capsules, 140 mg****Pharmacyclics, Inc.****Xiao-Hong Chen, Ph.D.
Donghao (Robert) Lu, Ph.D.****Office of New Drug Quality Assessment
Division of New Drug Quality Assessment I****CMC Review of NDA 205-552****For the Division of Oncology Drug Products I (HFD-150)**

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Chemistry Review Data Sheet

1. NDA 205-552
2. REVIEW #1:
3. REVIEW DATE: 13-SEPT-2013
4. REVIEWER: Donghao (Robert) Lu, Ph.D. (Drug substance)
Xiao-Hong Chen, Ph.D. (Drug product)
5. PREVIOUS DOCUMENTS:

Previous Documents

Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Document Date

Original NDA submission	28-Jun-2013
Amendment SN0018	09-Aug-2013
Amendment SN0021	13-Aug-2013
Amendment SN0027	23-Aug-2013
Amendment SN0029	29-Aug-2013

7. NAME & ADDRESS OF APPLICANT:

NAME:

Pharmacyclics, Inc.

ADDRESS:

995 East Arques Avenue,
Sunnyvale, CA 94085

REPRESENTATIVE:

Christine Salido, Exec. Director,
Regulatory Affairs

TELEPHONE:

(408) 215-3476

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Imbruvica®
- b) Non-Proprietary Name (USAN): ibrutinib

- c) Code Name/# PCI-32765, JNJ 54179060
d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: 1
 - Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: Filed 505(b)(1)

10. PHARMACOL. CATEGORY: A potent small-molecule covalent inhibitor of Bruton's tyrosine kinase

11. DOSAGE FORM: Capsule

12. STRENGTH/POTENCY: 140 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC

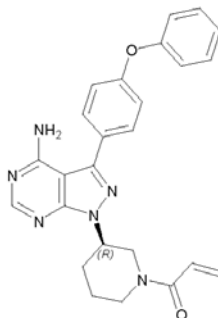
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Name (USAN, INN): Ibrutinib
Name (CAS): 1-((3R)-3-[4-amino-3-(4-phenoxyphenyl)-1Hpyrazolo[3,4-d]pyrimidin-1-yl]piperidin-1-yl)prop-2-en-1-one
Other Name: 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1Hpyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one
(CAS) Registry Num: 936563-96-1
Mol. Formula: C₂₅H₂₄N₆O₂
Mol. Wt.: 440.50
Structural Formula:



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENT
(b) (4)	III		(b) (4)	4	Adequate	8-2-2013	USP<661> and FAR (21CFR177.1520) submitted in NDA
	III		4	Adequate	8-2-2013	USP<661> and FAR (21CFR177.1520) submitted in NDA	
	III		3	Adequate	1-31-2012	Reviewed by Gene Holbert	
	III		4	Adequate	8-2-2013	USP<661> and FAR (21CFR177.1210) submitted in NDA	
	III		3	Adequate	9-21-2012	Reviewed by Raymond P. Frankewich	

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Supporting Documents:

Doc #	OWNER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS

C. Related Documents:

DOCUMENT	APPLICATION	OWNER	DESCRIPTION/COMMENT

	NUMBER		
IND	102,688	Pharmacyclics, Inc.	Original IND submitted on 07-Oct-2008.

18. CONSULTS/CMC-RELATED REVIEWS:

CONSULTS	RECOMMENDATION	DATE	REVIEWER
EES	Pending	13-SEP-2013	Office of Compliance
Biopharmaceutics	Pending	13-SEP-2013	John Duan, Ph.D.
Proprietary Name	Acceptable	16-AUG-2013	Sue Kang
Methods Validation	Pending	23-JUL-2013	A methods validation request was sent and the evaluation results are pending. It should be noted that the approvability of the NDA is not dependent upon the results.
EA (Categorical exclusion)	Acceptable	13-SEP-2013	Xiao Hong Chen
Microbiology	Acceptable	9-JUL-2013	Bryan S. Riley, Ph.D.

The Chemistry Review for NDA 205-552

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From a CMC perspective, this application is recommended for Approval pending the overall recommendation for the pre-approval inspection from the Office of Compliance.

In addition, the biopharmaceutics review of the dissolution specification is still pending. Review of the package insert labeling and container/carton labels are under way. The following comment should be included in the action letter:

Based on the available stability data an 24-month expiry dating is granted for Imbruvica® ibrutinib capsules stored at temperature of 20°C to 25°C (68°F to 77°F) with excursions permitted between 15°C and 30°C (between 59°F and 86°F).

B. Recommendation on Post Marketing Requirements, Post Marketing Commitments, Agreements, and/or Risk Management Steps, if Approvable.

N/A.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Product

Ibrutinib is being co-developed by Pharmacyclics, Inc. (Pharmacyclics) and Janssen Research & Development, LLC (Janssen R&D) as an orally administered anticancer agent for the treatment

(b) (4) mantle cell lymphoma (MCL) (b) (4)
The drug product is an immediate-release opaque white size 0 hard gelatin capsule for oral administration, containing 140 mg of ibrutinib drug substance and commonly used compendial excipients such as microcrystalline cellulose, croscarmellose sodium, sodium lauryl sulfate and magnesium stearate, etc. The drug product is packaged in two configurations: 160 cc HDPE bottles with (b) (4) child-resistant closure containing 90 capsules and 200 cc HDPE bottles containing 120 capsules.

The drug product is manufactured by the contract manufacturer, (b) (4) The intended commercial scale is (b) (4) capsules (b) (4) total weight). Manufacturing of Ibrutinib Capsules uses (b) (4)

(b) (4)

The drug product specifications consist of description, identity, assay, individual and total degradation products, (b) (4), content uniformity, dissolution and microbial limits. The HPLC method used for identity, assay and content uniformity is the same method that is used for the drug substance assay. The acceptance limits for the three identified degradation products have been qualified and/or below the safety threshold for oncology drugs per pharm/tox review team. The acceptance limits for degradation products (b) (4) per FDA's comments. Dissolution specification is evaluated by biopharmaceutics reviewer, Dr. John Duan. His review is still ongoing. Microbial test is reviewed by microbiology reviewer, Dr. Bryan Riley; and an acceptable recommendation was made by his review (July 8, 2013).

Stability studies for drug product are performed. Stability data for 3 registration batches, 7 primary stability batches and one supportive stability batch are submitted. The drug product appears to be fairly stable. Only a slight increasing trend of degradation products (b) (4) and a slight decreasing trend of assay have been observed. Up to 24 months long term primary and supportive stability data are well within the specification. Six months of accelerated stability data also conform to the specification with a clearer trending for degradation products and assay value. Photostability study conducted per ICH guidelines showed that the drug product is not light sensitive. Based on the primary and supportive stability data the shelf life of 24 months stored at "storage temperature at 20°C to 25°C (68°F to 77°F) with excursions permitted between 15°C and 30°C (between 59°F and 86°F) can be granted.

Drug Substance

The drug substance is Ibrutinib. The chemical name is 1-((3R)-3-[4-amino-3-(4-phenoxyphenyl)-1Hpyrazolo [3,4-d]pyrimidin-1-yl]piperidin-1-yl)prop-2-en-1-one. It has a molecular formula of C₂₅H₂₄N₆O₂ and its molecular weight is 440.50.

Data from the studies of elemental analysis, UV, IR, NMR and MS demonstrated that the structure was adequately defined. The synthesis route and the use of reagents are adequate for the manufacturing of the ibrutinib drug substance.

The impurities detected during the development and synthesis of the drug substance were evaluated. Analytical methods were developed for the control of the impurities listed in the submission. Comprehensive information for all the impurities at the starting material level, at the intermediate level and at the final synthesis level was adequately presented.

Ibrutinib was subjected to heat, heat and moisture, light, and chemical stresses. The drug substance was physically and chemically stable based on evaluation of the testing data. The drug substance has a retest period of (b) (4) months.

B. Description of How the Drug Product is Intended to be Used

Imbruvica® is administered by orally once daily for 560 mg (four 140 mg capsules) for MCL (Mantel cell lymphoma) patients (b) (4)

(b) (4) Capsules should be taken orally with a glass of water without being opened, broken or chewed.

C. Basis for Approvability Recommendation

From a CMC perspective, Pharmacyclics, Inc. has submitted sufficient and appropriate information to support the approval of the drug product. There were several CMC concerns that were sent to the sponsor during the review process. Pharmacyclics has adequately addressed these CMC comments. Their responses and the CMC evaluations for these responses are described at the end of this document.

III. Administrative

A. Reviewer's Signature

See appended electronic signature page.

B. Endorsement Block

Reviewer Name/Date: Xiao-Hong Chen, Ph.D.
Donghao (Robert) Lu, Ph.D.
Branch Chief Name/Date: Ali Al Hakim, Ph.D.

C. CC Block

Diane Hanner/OHOP/DHP/Regulatory PM
Janice Brown/ONDQA/CMC Lead
Jewell Martin/ONDQA/PM
Donghao Lu/ONDQA/DNDQA I Branch II
Ali Al Hakim/ONDQA/DNDQA I/Branch Chief
Ramesh Sood/ONDQA/DNDQA I Acting Director

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

XIAO H CHEN
09/23/2013

DONGHAO R LU
09/23/2013

ALI H AL HAKIM
09/23/2013

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)**

NDA Number:	Supplement Number and Type:	Established/Proper Name:
205552	Original NDA	Ibrutinib Capsules
Applicant:	Letter Date:	Stamp Date:
Pharmacyclics, Inc.	28-Dec-2013	28-Jun-2013

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	Yes	No	Comment
1.	Is the CMC section organized adequately?	X		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	X		
3.	Are all the pages in the CMC section legible?	X		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		

B. FACILITIES*				
	PARAMETER	YES	NO	COMMENT
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	X		
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? This question is not applicable for synthesized API.			NA
7.	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	X		

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)**

B. FACILITIES*				
	PARAMETER	YES	NO	COMMENT
8.	Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	X		
9.	Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	X		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	X		

* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESMENT				
	Parameter	Yes	No	Comment
11.	Has an environmental assessment report or categorical exclusion been provided?	X		

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)**

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	Yes	No	Comment
12.	Does the section contain a description of the DS manufacturing process?	X		
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	X		
14.	Does the section contain information regarding the characterization of the DS?	X		
15.	Does the section contain controls for the DS?	X		
16.	Has stability data and analysis been provided for the drug substance?	X		
17.	Does the application contain Quality by Design (QbD) information regarding the DS?	X		
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?	X		
E. drug product (dp)				
	Parameter	Yes	No	Comment
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	X		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	X		
21.	Is there a batch production record and a proposed master batch record?	X		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	X		
23.	Have any biowaivers been requested?			Refer to Biopharm filing review
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	X		
25.	Does the section contain controls of the final drug product?	X		
26.	Has stability data and analysis been provided to support the requested expiration date?	X		Expiry will be determined by primary reviewers in ONDQA
27.	Does the application contain Quality by Design (QbD) information regarding the DP?	X		
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		X	

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)**

F. METHODS VALIDATION (MV)				
	Parameter	Yes	No	Comment
29.	Is there a methods validation package?	X		

G. MICROBIOLOGY				
	Parameter	Yes	No	Comment
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?	NA		

H. MASTER FILES (DMF/MAF)				
	Parameter	Yes	No	Comment
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	X		

I. Labeling				
	Parameter	Yes	No	Comment
32.	Has the draft package insert been provided?	X		
33.	Have the immediate container and carton labels been provided?	X		

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)**

J. FILING CONCLUSION				
	Parameter	Yes	No	Comment
34.	IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?	X		
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.			N.A.
36.	Are there any potential review issues to be forwarded to the Applicant for the 74-day letter?		X	

{See appended electronic signature page}

Janice Brown Date: See electronic date stamp
 Pharmaceutical Assessment Lead or CMC Lead / CMC Reviewer
 Division of Pre-Marketing Assessment 1
 Office of New Drug Quality Assessment

{See appended electronic signature page}

Ali Al Hakim, Ph.D. Date: See electronic date stamp
 Chief, Branch 2
 Division of Pre-Marketing Assessment 1
 Office of New Drug Quality Assessment

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/s/

JANICE T BROWN
07/25/2013

ALI H AL HAKIM
07/25/2013